104. (New) A method of claim 102, wherein the chemical group is selected from the group consisting of: an amino group, a carboxy group, a thiol group, a malemido group, an iodoacetamido group, a vinylsulfone group, an aldehyde group, a hydrazine group, a ketone group, and a cyanure chloride group.

REMARKS

I. The Amendments Herein

By this Amendment, claims 1-58 are canceled, claims 76-80 have been amended and claims 81-104 added.

No new matter has been added by the amendments herein. The amendment to claim 78 corrects a minor typographical error. The amendments to claims 76, 77, 79, and 80 specify that the protein is attached to the lipidic microparticle (or to one of the specific embodiments of a lipidic microparticle: a liposome, lipid:nucleic acid complex, lipid:drug complex, or microemulsion droplet) through a linker molecule by means of a chemical group, which chemical group prior to the conjugation is reactive with a component of the lipidic microparticle. These amendments are supported throughout the specification, including page 14, lines 25-27, which specify that the lipidic microparticle may contain molecules reactive with the linker active group, and claims 76-80 as filed. New claim 81 adds the same language to original claim 78. New claims 82 and 83 claim the compositions without reciting the process of claim 59.

New claims 84-88 recite lipidic microparticles (or one of the specific embodiments thereof) conjugated to a protein by the method of claim 59, wherein the microparticle does not bear unconjugated linkers. These new claims are supported throughout the specification, including page 14, lines 23-24. New claims 89 and 90 claim such compositions without reciting product by process language.

New claims 91-95 recite lipidic microparticles (or one of the specific embodiments thereof) conjugated to two or more protein species by the method of claim 59, wherein the protein species are conjugated to the microparticle through a functional group, which functional group is the same for each protein species. These new claims are supported throughout the specification, including page 14, lines 19-22. Lines 21-22, in particular, state

that more than one kind of protein can be attached to the surface of the microparticle. Applicants have used the term "species" rather than "kind" to denote that two different types of proteins are conjugated to the microparticle, since "species" is the term more commonly used in the art.

Applicants further observe that the specification does not specifically state that the two proteins could be attached by the same functional group. Applicants maintain that a person of ordinary skill in the art (typically, a Ph.D. level chemist) would readily recognize that the methods of the invention provide this advantage. This advantage does not need to be set forth in the specification. The Federal Circuit has repeatedly held that the specification "need not teach, and *preferably omits,* what is well known in the art." *See, e.g., In re Buchner,* 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) (emphasis added); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 at 94 (Fed. Cir. 1986). New claims 95 and 96 claim the compositions without reciting product by process language.

New claim 98 is a new claim dependent on claim 59. The new claim provides that two or more protein species are attached to the lipidic microparticle. This claim is supported throughout the specification, including page 14, lines 19-22. Lines 21-22, in particular, state that more than one kind of protein can be attached to the surface of the microparticle. Applicants once again have used the term "species" rather than "kind" to denote that two different types of proteins are conjugated to the microparticle, since "species" is the term more commonly used in the art. New claim 99 is dependent on 98. It provides that the protein species can be independently selected an antibody, an Fab', and a single-chain Fv antibody. The claim is supported throughout the specification, including page 10, lines 12-16, page 14, lines 19-22, page 35, lines 22-23, and claims 65-67 as originally presented. New claim 100 is dependent on claim 99, and is supported throughout the specification, including page 10, lines 12-16.

New claim 101 is supported throughout the specification, including claim 59, and page 14, lines 21-22. New claim 102 is supported throughout the specification, including page 14, lines 25-27. New claim 103 is supported by that same passage and claims 61-64 as originally presented. Finally, new claim 104 is supported by the same passage and by page 35, lines 16-19.

II. The Invention

The invention provides new methods of conjugating proteins to lipidic microparticles. Additionally, the invention provides compositions of proteins conjugated to lipidic microparticles that cannot be made by techniques previously known in the art.

III. The Information Disclosure Statement

Applicants call the Examiner's attention to the Information Disclosure Statement (IDS) filed on January 20, 2000, citing three groups of references. The first group, reference AD, consists of Zalipsky et al., Bioconjugate Chem., 8:111-118 (1997). The second group, references AB and AC, were cited in international search reports relating to parent case 08/967,791, filed November 11, 1997, or relating to the present case. The third group of references, AA and AE to AX, were cited to or by the Patent and Trademark Office in connection with the parent, '791, case. Applicants respectfully request that the references cited in the IDS be made of record and be given the Examiner's careful consideration.

IV. The Office Action

Applicants note with appreciation the indication in the Office Action that claims 59-75 are allowable over the art of record. The Action, however, also rejects claims 76-80 on two grounds. Applicants amend in part and traverse the rejections, as set forth below.

A. Rejection of the claims as anticipated

The Action rejects claims 76, 77, 79 and 80 as anticipated under 35 U.S.C. § 102(b) by Hansen et al., Biochimica et Biophysica Acta 1239:133-144 (1995) (hereafter "Hansen"). According to the Action, Hansen teaches liposomes in which a hydrophobic domain of a linker is attached to the hydrophilic domain of a linker which is attached to a protein through a linkage comprising the residue of a reactive group. According to the Action, the compositions of Hansen therefore satisfy the claim limitations and could have been made by the methods of the present invention.

The Applicants do not necessarily agree with the Action's conclusions. Nonetheless, to expedite prosecution, claims 76, 77, 79, and 80 have been amended, and claims 81-96 have been added, to claim certain groups of conjugated lipidic microparticles which are provided by the present invention, but which could not be made (and thus cannot be anticipated or rendered obvious) by Hansen. For the Examiner's convenience, the groups will be discussed in turn.

1. Lipidic microparticles conjugated to proteins by means of a chemical group which prior to conjugation is reactive with a component of the lipidic microparticle.

The first group, claims 76, 77, 79, and 80 as amended, concern lipidic microparticles conjugated to proteins by means of a chemical group which prior to conjugation is reactive with a component of the lipidic microparticle. Such microparticles cannot be made by the method taught by Hansen. The conjugates in Hansen are made by first inserting into the lipidic microparticle the hydrophobic moiety of the linker, which contains at the contralateral end a reactive group which is then reacted with a reactive group on the protein to produce the desired conjugate. The use of reactive groups which would react with a component of the lipidic microparticle is precluded since the reactive group will either react with the component of the lipidic microparticle before the linker inserts or, since the linker molecules are not rigid, will react with the reactive group of the lipidic microparticle after insertion. In either event, the reactive group is then unavailable to react with the protein which the practitioner desires to conjugate. By contrast, the present invention permits use of reactive groups which are a component of the microparticle. This advantage of the invention is specifically noted in the specification at page 14, lines 25-27. Since microparticles of this kind can be physically distinguished from those taught by Hansen, claims 82 and 83 claim these compositions without recitation of product by process language.

2. Lipidic microparticles conjugated to proteins wherein the microparticle does not bear unconjugated linkers

The lipidic microparticles made by prior art techniques, such as Hansen, result in the presence of large amounts of unconjugated linkers. The Examiner will recall that Hansen's method depends on first inserting the hydrophobic moiety (linker) into the microparticle and then reacting it with the protein. Thus, unless the reaction between the linker and the protein is 100% efficient, the Hansen method results in excess, unconjugated linker. Indeed, Hansen teaches that the linker needs to be present in amounts nine times that of the protein to be conjugated or the efficiency of conjugation will be sharply and adversely affected. See, Hansen, at page 140, left column, first full paragraph ("corresponding to an Ab to linker molar ratio of about 1:10 or lower." (emphasis added)) and Figure 3.

In contrast, as taught in the present specification, "if the protein-linker conjugate is purified before insertion into a particle surface, the particle will not bear unconjugated linkers." Specification, at page 15, lines 23-24. It should be noted that the specification further teaches that the conjugate can be purified of excess linker and any unconjugated protein by salting-out, dialysis, chromatography, and other methods known in the art. Specification, at pages 35-36, bridging sentence. The Examiner will appreciate that each of these art-recognized methods will generally leave a small number of molecules of linker or unconjugated protein present. Thus, the statement that the particle "will not bear unconjugated linker" must be read in light of the further teachings regarding the methods contemplated for removing unconjugated linker. It is clear that the small incidental number of linker molecules left after these purification methods will not interfere with the intended reactions and are unimportant to the practice of the invention, in contrast to the 9-fold excess of unconjugated linker to protein Hansen teaches is desirable.

3. Lipidic microparticles conjugate to two or more protein species wherein each protein is conjugated by the same functional group

The third group, claims 91-95, concern lipidic microparticles conjugated to two or more proteins, each of which is conjugated by the same functional group. For clarity, the claims refer to "protein species" to emphasize that they refer to two or more different proteins

and not merely to two or more molecules of the same protein. This is directly supported by the specification at page 14, lines 21-22, which states that one advantage of the present invention is the ability to attach more than one protein, and to do so in precise proportions to one another. The claims further recite that the proteins are attached by the same functional group. This is possible by the methods of the invention, since the proteins can be separately reacted with the linkers. This permits introducing the protein species in precise proportions. In contrast, the Hansen method is incapable of introducing proteins in precise proportions using the same functional group to react the proteins since it is known that different proteins (even different antibodies of the same class) have different reactivities.

Hansen does not teach every element of the invention as presented in claimed in claims 91-95. As the Examiner is aware, a reference must teach every aspect of the claimed invention to constitute a proper reference for purposes of § 102 (b). *See, e.g.*, MPEP 706.02(a), 7th Ed. (July 1998) ("for anticipation under 35 U.S.C. 102, the reference must teach **every** aspect of the claimed invention") (emphasis added). Hansen thus is not a proper reference against claims 91-95 for purposes of § 102 (b) and cannot provide the basis for rejecting them under this section.

B. The rejection of claim 78 under 35 U.S.C. § 103(a)

The Action rejects claim 78 under 35 U.S.C. § 103(a) as obvious over Hansen. According to the Action, Hansen teaches generally the generation of liposome complexes and asserts that it is "apparent" that the liposome complexes of Hansen could have been assembled by the methods recited in claim 78. Further according to the Action, the specification "admit" that page 2 that it was "well-known in the art to employ liposomes for the delivery of nucleic acids to cells." Action, at page 5. Applicants traverse.

Applicants observe that page 15, lines 5-7, of the specification state: "It is also recognized that after complexation, the lipid:nucleic acid complex may no longer exist as a true vesicle and therefore is not generally regarded as a liposome." This is because these complexes have a variety of different structures which are not equivalent to the vesicular structures of liposomes. Thus, the syllogism which the Action attempts to suggest by asserting

the correspondence of liposomes and lipid:nucleic acid complexes is not generally considered true in the art.

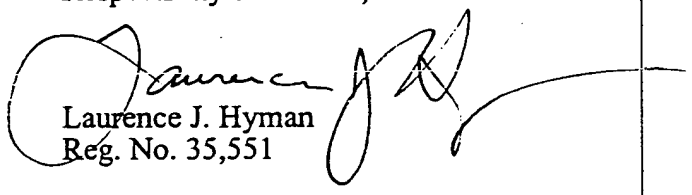
The Action's position is further incorrect because the formation of lipid:DNA complexes requires the close apposition of the DNA molecule to the lipid, which is not generally possible if the conjugation linker is introduced to the lipid by the method of Hansen since the PEG will interfere with the necessary proximity of the lipid and the DNA. For example, the interaction of liposomes made according to the method of Hansen with plasmid DNA would be impeded by the presence of the hydrophobic domains of the linkers which, under the method of Hansen, would already be present on the surface of the liposome prior to the attempted complexation. In contrast, the present invention demonstrates that such complexes can be readily made by the methods of the invention. See, specification at Examples 15 and 16, at pages 54-56. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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